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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	DEC 01	ChemPort single article sales feature unavailable
NEWS 3	JUN 01	CAS REGISTRY Source of Registration (SR) searching enhanced on STN
NEWS 4	JUN 26	NUTRACEUT and PHARMAML no longer updated
NEWS 5	JUN 29	IMSCOPROFILE now reloaded monthly
NEWS 6	JUN 29	EPFULL adds Simultaneous Left and Right Truncation (SLART) to AB, MCLM, and TI fields
NEWS 7	JUL 09	PATDPAFULL adds Simultaneous Left and Right Truncation (SLART) to AB, CLM, MCLM, and TI fields
NEWS 8	JUL 14	USGENE enhances coverage of patent sequence location (PSL) data
NEWS 9	JUL 27	CA/CAplus enhanced with new citing references
NEWS 10	JUL 16	GBFULL adds patent backfile data to 1855
NEWS 11	JUL 21	USGENE adds bibliographic and sequence information
NEWS 12	JUL 28	EPFULL adds first-page images and applicant-cited references
NEWS 13	JUL 28	INPADOCDB and INPAFAMDB add Russian legal status data
NEWS 14	AUG 10	Time limit for inactive STN sessions doubles to 40 minutes
NEWS 15	AUG 18	COMPENDEX indexing changed for the Corporate Source (CS) field
NEWS 16	AUG 24	ENCOMPLIT/ENCOMPLIT2 reloaded and enhanced
NEWS 17	AUG 24	CA/CAplus enhanced with legal status information for U.S. patents
NEWS 18	SEP 09	50 Millionth Unique Chemical Substance Recorded in CAS REGISTRY
NEWS 19	SEP 11	WPIDS, WPINDEX, and WPIX now include Japanese FTERM thesaurus

NEWS EXPRESS MAY 26 09 CURRENT WINDOWS VERSION IS V8.4,
AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2009.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS LOGIN Welcome Banner and News Items

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 17:01:14 ON 17 SEP 2009

=> file registry
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY     SESSION
FULL ESTIMATED COST                                         0.22        0.22

FILE 'REGISTRY' ENTERED AT 17:01:24 ON 17 SEP 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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COPYRIGHT (C) 2009 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   16 SEP 2009  HIGHEST RN 1185221-67-3
DICTIONARY FILE UPDATES:  16 SEP 2009  HIGHEST RN 1185221-67-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 26, 2009.

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> s pmcol
L1             0 PMCOL

=>
Uploading C:\Program Files\Stnexp\Queries\10789835specie2.str
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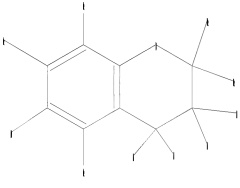

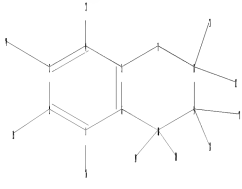

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chain nodes :
11  12  13  14  15  16  17  18  19  20
ring nodes :
1  2  3  4  5  6  7  8  9  10
chain bonds :
1-16  2-15  3-14  4-13  8-11  8-12  9-17  9-18  10-19  10-20
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  5-7  6-10  7-8  8-9  9-10
exact/norm bonds :
```

```
2-15  5-7  6-10  7-8  8-9  9-10
exact bonds :
1-16  3-14  4-13  8-11  8-12  9-17  9-18  10-19  10-20
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS  18:CLASS
19:CLASS  20:CLASS



L2      STRUCTURE UPLOADED

=> d l2
L2 HAS NO ANSWERS
L2              STR
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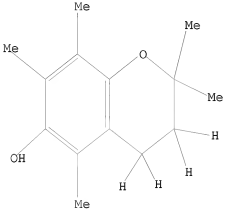


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Structure attributes must be viewed using STN Express query preparation.


=> s l2
SAMPLE SEARCH INITIATED 17:02:14 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      677 TO ITERATE

100.0% PROCESSED      677 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       11979 TO    15101
PROJECTED ANSWERS:              0 TO        0

L3            0 SEA SSS SAM L2

=> s l2 sss
SAMPLE SEARCH INITIATED 17:02:18 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      677 TO ITERATE

100.0% PROCESSED      677 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01
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FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         11979 TO    15101
PROJECTED ANSWERS:                0 TO        0

L4            0 SEA SSS SAM L2

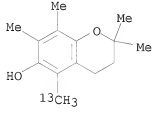
=> s l2 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 185.40 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 17:02:27 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    13670 TO ITERATE

100.0% PROCESSED    13670 ITERATIONS                                 12 ANSWERS
SEARCH TIME: 00.00.01

L5           12 SEA SSS FUL L2

=> d l5 1-12

L5   ANSWER 1 OF 12  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   937377-46-3  REGISTRY
ED   Entered STN:  15 Jun 2007
CN   2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,7,8-tetramethyl-5-(methyl-13C)-  (CA
     INDEX NAME)
MF   C14 H20 O2
SR   CA
LC   STN Files:   CA, CAPLUS, CASREACT
```

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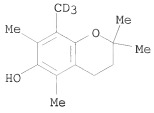
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

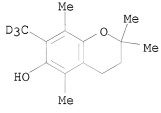
               1 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5   ANSWER 2 OF 12  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   794535-00-5  REGISTRY
ED   Entered STN:  08 Dec 2004
CN   2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7-tetramethyl-8-(methyl-d3)- (9CI)
     (CA INDEX NAME)
MF   C14 H17 D3 O2
SR   CA
LC   STN Files:   CA, CAPLUS
```



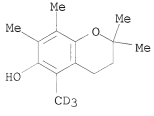
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 3 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 153401-24-2 REGISTRY
ED Entered STN: 03 Mar 1994
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,8-tetramethyl-7-(methyl-d3)- (9CI) (CA INDEX NAME)
MF C14 H17 D3 O2
SR CA
LC STN Files: CA, CAPLUS



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 4 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 153401-23-1 REGISTRY
ED Entered STN: 03 Mar 1994
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,7,8-tetramethyl-5-(methyl-d3)- (9CI) (CA INDEX NAME)
MF C14 H17 D3 O2
SR CA
LC STN Files: CA, CAPLUS



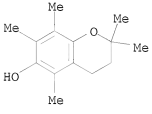
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 5 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 117657-15-5 REGISTRY

ED Entered STN: 18 Nov 1988
CN Antimonate(1-), hexachloro-, (OC-6-11)-, salt with
    3,4-dihydro-2,2,5,7,8-pentamethyl-2H-1-benzopyran-6-ol (1:1) (9CI) (CA
    INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl-, radical ion(1+),
    (OC-6-11)-hexachloroantimonate(1-) (9CI)
MF C14 H20 O2 . Cl6 Sb
SR CA
LC STN Files: CA, CAPLUS

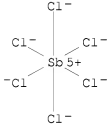
    CM 1

    CRN 52471-80-4
    CMF C14 H20 O2
    CCI RIS



    CM 2

    CRN 17949-89-2
    CMF Cl6 Sb
    CCI CCS

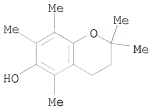


            1 REFERENCES IN FILE CA (1907 TO DATE)
            1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 97657-24-4 REGISTRY
ED Entered STN: 18 Aug 1985
CN 6-Chromanol, 2,2,5,7,8-pentamethyl-, compd. with piperazine (2:1) (7CI)
    (CA INDEX NAME)
MF C14 H20 O2 . 1/2 C4 H10 N2
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, USPATOLD
        (*File contains numerically searchable property data)

    CM 1

CRN 950-99-2
CMF C14 H20 O2



CM 2

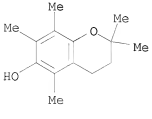
CRN 110-85-0
CMF C4 H10 N2

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 71490-90-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1,1,2,2-Ethenetetracarbonitrile, compd. with 3,4-dihydro-2,2,5,7,8-pentamethyl-2H-1-benzopyran-6-ol (1:?) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl-, compd. with ethenetetracarbonitrile (9CI)
CN Ethenetetracarbonitrile, compd. with 3,4-dihydro-2,2,5,7,8-pentamethyl-2H-1-benzopyran-6-ol (9CI)
MF C14 H20 O2 . x C6 N4
LC STN Files: CA, CAPLUS

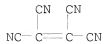
CM 1

CRN 950-99-2
CMF C14 H20 O2



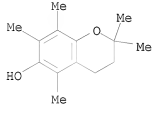
CM 2

CRN 670-54-2
CMF C6 N4



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 52471-80-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl-, radical ion(1+) (9CI) (CA INDEX NAME)
MF C14 H20 O2
CI COM, RIS
LC STN Files: CA, CAPLUS



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

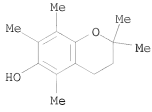
L5 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 34033-59-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN 6-Chromanol, 2,2,5,7,8-pentamethyl-, phosphate (3:1) (8CI) (CA INDEX NAME)
MF C14 H20 O2 . 1/3 H3 O4 P
LC STN Files: CA, CAPLUS

CM 1

CRN 7664-38-2
CMF H3 O4 P

CM 2

CRN 950-99-2
CMF C14 H20 O2

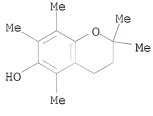


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

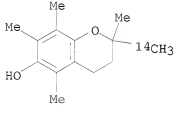
L5 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 33897-44-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN 6-Chromanol, 2,2,5,7,8-pentamethyl-, dimer (8CI) (CA INDEX NAME)
MF (C14 H20 O2)2
CI PMS

CM 1

CRN 950-99-2
CMF C14 H20 O2



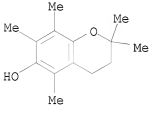
L5 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 21060-77-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN 6-Chromanol, 2,5,7,8-tetramethyl-2-methyl-14C- (8CI) (CA INDEX NAME)
MF C14 H20 O2
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 12 OF 12 REGISTRY COPYRIGHT 2009 ACS on STN
RN 950-99-2 REGISTRY
ED Entered STN: 16 Nov 1984

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 6-Chromanol, 2,2,5,7,8-pentamethyl- (6CI, 7CI, 8CI)
OTHER NAMES:
CN α-C-1-Chromanol
CN 2,2,5,7,8-Pentamethyl-6-chromanol
CN 2,2,5,7,8-Pentamethyl-6-hydroxychroman
CN 6-Hydroxy-2,2,5,7,8-pentamethylchroman
CN Chroman C1
CN Chromane C1
CN Chromanol
CN NSC 226236
CN PMC
CN TMC 5
MF C14 H20 O2
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, MEDLINE, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL, USPATOLD
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

438 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
438 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	216.79	217.01

FILE 'CAPLUS' ENTERED AT 17:02:58 ON 17 SEP 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

```
FILE COVERS 1907 - 17 Sep 2009  VOL 151 ISS 12
FILE LAST UPDATED: 16 Sep 2009  (20090916/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Jun 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Jun 2009

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2009.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.

The ALL, BIB, MAX, and STD display formats in the CA/CAplus family
of databases have been updated to include new citing references
information.  This enhancement may impact record import into
database management software.  For additional information, refer
to NEWS 9.

=> d his

     (FILE 'HOME' ENTERED AT 17:01:14 ON 17 SEP 2009)

     FILE 'REGISTRY' ENTERED AT 17:01:24 ON 17 SEP 2009
L1             0 S PMCOL
L2               STRUCTURE UPLOADED
L3             0 S L2
L4             0 S L2 SSS
L5            12 S L2 FULL

     FILE 'CAPLUS' ENTERED AT 17:02:58 ON 17 SEP 2009

=> s l5
L6           442 L5

=> s l6 and (?cancer? or ?tumor? or ?tumour? or ?neoplasm?)
        472104 ?CANCER?
        744938 ?TUMOR?
          6557 ?TUMOUR?
          6557 ?TUMOUR?
        745320 ?TUMOR?
                 (?TUMOR? OR ?TUMOUR?)
          6557 ?TUMOUR?
        744938 ?TUMOR?
        744938 ?TUMOR?
        745320 ?TUMOUR?
                 (?TUMOUR? OR ?TUMOR?)
        579147 ?NEOPLASM?
L7            16 L6 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8            16 DUP REM L7 (0 DUPLICATES REMOVED)

=> d l8 1-16 ibib abs hitstr

L8   ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2008:224063  CAPLUS
DOCUMENT NUMBER:          148:285190
```

TITLE: Tricyclic compound derivatives useful in the treatment of neoplastic diseases, inflammatory disorders and immunomodulatory disorders

INVENTOR(S): Gregor, Vlad Edward; Liu, Yahua; Anikin, Alexey; McGee, Danny Peter Claude; Mikel, Charles; McGrath, Douglas Eric; Vavilala, Goverdhan Reddy; Pickens, Jason C.; Kadushkin, Alexander; Thiruvazhi, Mohan Santhanam; Zozulya, Sergey; Vairagoundar, Rajendran; Zhu, Tong; Chucholowski, Alexander; Webb, Thomas R.; Jiang, Luyong; Gantla, Vidyasagar Reddy; Yan, Zheng

PATENT ASSIGNEE(S): Chembridge Research Laboratories, Inc., USA

SOURCE: PCT Int. Appl., 339pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008021369	A2	20080221	WO 2007-US18002	20070813
WO 2008021369	A3	20080529		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20080171769	A1	20080717	US 2007-891604	20070810
AU 2007284542	A1	20080221	AU 2007-284542	20070813
CA 2660899	A1	20080221	CA 2007-2660899	20070813
EP 2066673	A2	20090610	EP 2007-836819	20070813
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				

PRIORITY APPLN. INFO.: US 2006-837652P P 20060814
WO 2007-US18002 W 20070813

OTHER SOURCE(S): MARPAT 148:285190

GI

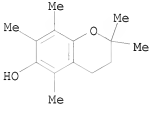
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Provided are compds. of formula I or a stereoisomer, tautomer, salt, hydrate, or prodrug thereof, capable of modulating tyrosine kinases, compns. comprising the compds. and methods of their use. Compds. of formula I wherein each W1 - W6 are independently C and N, with the proviso that then W1 - W6 is N, the corresponding substituent X1 - X6 is absent; each X1 - X3, X5 and X6 are independently H, OH, halo, (un)substituted lower alkyl, (un)substituted lower alkoxy, (un)substituted acylamino, etc.; X4 is H, OH, halo, CF3, OCF3, (un)substituted alkyl, (un)substituted alkenyl, (un)substituted alkynyl, etc.; Y1 and Y2 are independently (un)substituted (CH2)0-4 alkyl, CO, CS, C=NH, and derivs., SO2 and CF2; R1 is (un)substituted heterocyclyl, heterocyclylalkyl, heteroaryl,

heteroarylalkyl, etc.; and their stereoisomers, tautomers, salts, hydrated and prodrugs thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their tyrosine kinase modulatory activity (data given).

IT 950-99-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of tricyclic compound derivs. as tyrosine kinase modulators useful in treatment and prevention of neoplastic, inflammatory, immune and other tyrosine kinase-related diseases)

RN 950-99-2 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



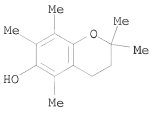
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L8 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:213340 CAPLUS
DOCUMENT NUMBER: 148:393733
TITLE: Strongylophorines: Natural Product Inhibitors of Hypoxia-Inducible Factor-1 Transcriptional Pathway
AUTHOR(S): Mohammed, Kaleem A.; Jadulco, Raquel C.; Bugni, Tim S.; Harper, Mary Kay; Sturdy, Megan; Ireland, Chris M.
CORPORATE SOURCE: Department of Medicinal Chemistry, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Journal of Medicinal Chemistry (2008), 51(5), 1402-1405
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rapidly increasing exptl. and clin. data provides evidence for the role of hypoxia inducible factor-1 (HIF-1) as a crucial mediator of tumor survival and progression. In our effort to identify inhibitors of the HIF-1 activation pathway, we screened fractions from marine invertebrates. Fractions from an extract of Petrosia (Strongylophora) strongylata potently inhibited the HIF-1 activation pathway. Strongylophorines 2, 3, and 8 isolated from the active fractions were responsible for the HIF-1 inhibition with EC50 values of 8, 13, and 6 μM, resp.

IT 950-99-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(strongylophorines as inhibitors of HIF1 transcriptional pathway)

RN 950-99-2 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)

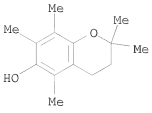


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:923577 CAPLUS
DOCUMENT NUMBER: 147:377567
TITLE: Antitumor agents. Syntheses and evaluation of dietary antioxidant-taxoid conjugates as novel cytotoxic agents
AUTHOR(S): Nakagawa-Goto, Kyoko; Yamada, Koji; Nakamura, Seikou; Chen, Tzu-Hsuan; Chiang, Po-Cheng; Bastow, Kenneth F.; Wang, Shao-Chun; Spohn, Bill; Hung, Mien-Chie; Lee, Fang-Yu; Lee, Fang-Chen; Lee, Kuo-Hsiung
CORPORATE SOURCE: Natural Products Research Laboratories, School of Pharmacy, University of North Carolina, Chapel Hill, NC, 27599, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2007), 17(18), 5204-5209
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 147:377567

AB Various dietary antioxidants, including vitamins, flavonoids, curcumin, and a coumarin, were conjugated with paclitaxel (I) through an ester linkage. The newly synthesized compds. were evaluated for cytotoxic activity against several human tumor cell lines as well as the corresponding normal cell lines. Interestingly, most tested conjugates selectively inhibited the growth of 1A9 (ovarian) and KB (nasopharyngeal) tumor cells without activity against other cell lines. Particularly, conjugates 16 and 20 were highly active against 1A9 (ED50 value of 0.005 μg/mL) as well as KB (ED50 values of 0.005 and 0.14 μg/mL, resp.) cells. The glycinate ester salt of vitamin E conjugated with I, appears to be a promising lead for further development as a clin. trial candidate as it exhibited strong inhibitory activity against Panc-1 (pancreatic cancer) with less effect on the related E6E7 (normal) cell line.

IT 950-99-2, 2,2,5,7,8-Pentamethyl-6-chromanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and evaluation of dietary antioxidant-taxoid conjugates as antitumor agents)
RN 950-99-2 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)

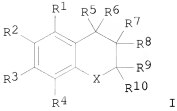


OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:894370 CAPLUS
DOCUMENT NUMBER: 145:299401
TITLE: Skin care and pharmaceutical compositions comprising chroman derivatives as lipoxygenase inhibitors
INVENTOR(S): Zhang, Wei; Chen, Jian; Boddupalli, Sekhar
PATENT ASSIGNEE(S): Galileo Pharmaceuticals, Inc, USA
SOURCE: U.S. Pat. Appl. Publ., 30pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060193797	A1	20060831	US 2006-349813	20060207
AU 2005328327	A1	20060908	AU 2005-328327	20051209
CA 2599352	A1	20060908	CA 2005-2599352	20051209
WO 2006093547	A2	20060908	WO 2005-US44360	20051209
WO 2006093547	A3	20070222		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
EP 1856040	A2	20071121	EP 2005-853306	20051209
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
JP 2008531558	T	20080814	JP 2007-557015	20051209
IN 2007KN02752	A	20070831	IN 2007-KN2752	20070726
MX 2007010327	A	20071016	MX 2007-10327	20070823
CN 101128423	A	20080220	CN 2005-80048717	20070824

PRIORITY APPLN. INFO.: US 2005-656644P P 20050225
WO 2005-US44360 W 20051209
OTHER SOURCE(S): CASREACT 145:299401; MARPAT 145:299401
GI



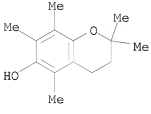
I

AB The present invention is concerned with certain novel derivs. of a compound, which may be useful in the manufacture of skin care and pharmaceutical compns. for treating disorders mediated by lipoxygenases and inflammatory skin conditions. Specifically, the invention is concerned with derivs. of a compound with formula (I): wherein X is O, S(O)0-2, or NR; R1 and R4 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, etc; R2 is selected from the group consisting of hydroxy, alkoxy, --O-alkenyl, etc; R3 is selected from the group consisting of alkyl, alkenyl, alkynyl, etc; R3 and R4 together with the atoms to which they are attached form a cycloalkyl ring, aryl ring or a heterocyclic ring; R5 and R6 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, etc; R7 and R8 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, etc; R9 is selected from the group consisting of hydrogen, alkyl and cycloalkyl; and R10 is alkyl or cycloalkyl.

IT 950-99-2, 2,2,5,7,8-Pentamethylchroman-6-ol
RL: RCT (Reactant); RACT (Reactant or reagent)
(skin care and pharmaceutical compns. comprising chroman derivs. as lipoxygenase inhibitors)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L8 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2006:101964 CAPLUS

DOCUMENT NUMBER: 144:184652

TITLE: Novel pathways in the etiology of cancer, and treatment methods

INVENTOR(S): Benz, Christopher C.

PATENT ASSIGNEE(S): Buck Institute for Age Research, USA

SOURCE: U.S. Pat. Appl. Publ., 49 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

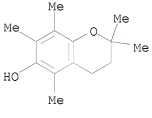
US 20060024691	A1	20060202	US 2005-90546		20050324
PRIORITY APPLN. INFO.:			US 2004-556774P	P	20040325
			US 2004-580534P	P	20040616
			US 2004-629691P	P	20041119

AB The invention pertains to the identification of two novel epithelial signaling pathways in ER-pos. breast cancers and the discovery that the cellular biol. and (likely also the clin. outcome) of ER-pos. breast cancer cells is unexpectedly altered when these signaling pathways are activated. The first pathway pertains to the discovery that NF-κB activation and/or DNA binding is implicated in the etiol. of ER-pos. breast (and other) cancers. The second pathway involves ligand-independent quinine-mediated ER activation by phosphorylation (e.g. on SER-118 and SER-167 residues of ER) and nuclear translocation of full-length (67 kDa) ER as well as the phorphorylating activation of a truncated and nuclear-localized ER variant (.apprx.52 kDa). Also disclosed are methods for identifying patients likely to respond to hormonal therapy and for selecting a therapeutic regimen for the treatment of cancer.

IT 950-99-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pathways in etiol. of cancer, and treatment methods)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



L8 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	2005:120717 CAPLUS
DOCUMENT NUMBER:	142:170094
TITLE:	Chroman-derived antiandrogens for treatment of androgen-mediated disorders
INVENTOR(S):	Thompson, Todd A.; Wilding, George
PATENT ASSIGNEE(S):	Wisconsin Alumni Research Foundation, USA
SOURCE:	PCT Int. Appl., 69 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005011658	A2	20050210	WO 2004-US5872	20040227
WO 2005011658	A3	20050519		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2004260631	A1	20050210	AU 2004-260631		20040227
AU 2004260631	B2	20090806			
CA 2517390	A1	20050210	CA 2004-2517390		20040227
US 20050192342	A1	20050901	US 2004-789835		20040227
EP 1596857	A2	20051123	EP 2004-785845		20040227
EP 1596857	B1	20081029			

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

AT 412411	T	20081115	AT 2004-785845		20040227
ES 2314451	T3	20090316	ES 2004-785845		20040227
HK 1088214	A1	20090612	HK 2006-105362		20060508
PRIORITY APPLN. INFO.:			US 2003-450510P	P	20030227
			WO 2004-US5872	A	20040227

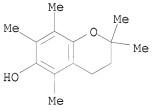
OTHER SOURCE(S): MARPAT 142:170094

AB Methods for the prevention and/or alleviation of androgen-mediated disorders treatable by administering a chroman-derived antiandrogen compound are provided by the invention. The invention further provides pharmaceutical and nutraceutical compns. containing chroman-derived antiandrogen compds. useful in the prevention and/or alleviation of androgen-mediated disorders, particularly prostate cancer. Compds. of the invention include e.g. 2,2,5,7,8-pentamethyl-6-chromanol.

IT 950-99-2, 2,2,5,7,8-Pentamethyl-6-chromanol
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chroman-derived antiandrogens for treatment of androgen-mediated disorders)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:618733 CAPLUS

DOCUMENT NUMBER: 141:174332

TITLE: Preparation of tocopherols, tocotrienols, other chroman and side chain derivatives for therapeutic use in the prevention and treatment of cancer

INVENTOR(S): Sanders, Bob G.; Kline, Kimberly; Hurley, Laurence; Gardner, Robb; Menchaca, Marla; Yu, Weiping; Ramanan, Puthucode N.; Liu, Shenquan; Israel, Karen

PATENT ASSIGNEE(S): Research Development Foundation, USA

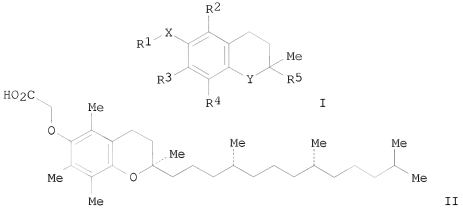
SOURCE: U.S., 48 pp., Cont.-in-part of U.S. Ser. No. 404,001. CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6770672	B1	20040803	US 2000-502592	20000211
US 6417223	B1	20020709	US 1999-404001	19990923
CN 1706838	A	20051214	CN 2005-10003855	19990923
CN 1318413	C	20070530		
CA 2399802	A1	20010816	CA 2001-2399802	20010209
WO 2001058889	A1	20010816	WO 2001-US4168	20010209
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1254130	A1	20021106	EP 2001-909008	20010209
EP 1254130	B1	20080102		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004504268	T	20040212	JP 2001-558439	20010209
NZ 520798	A	20040528	NZ 2001-520798	20010209
CN 1529701	A	20040915	CN 2001-807536	20010209
CN 1243000	C	20060222		
AU 2001236805	B2	20050714	AU 2001-236805	20010209
RU 2263672	C2	20051110	RU 2002-124135	20010209
IL 151108	A	20060801	IL 2001-151108	20010209
AT 382615	T	20080115	AT 2001-909008	20010209
US 20020107207	A1	20020808	US 2001-8066	20011105
US 6703384	B2	20040309		
US 20020156024	A1	20021024	US 2002-122019	20020412
US 6645998	B2	20031111		
KR 847678	B1	20080723	KR 2002-710387	20020810
US 20040235938	A1	20041125	US 2003-644418	20030820
US 7312232	B2	20071225		
US 20040097431	A1	20040520	US 2003-695275	20031028
US 7300954	B2	20071127		
US 20080119514	A1	20080522	US 2007-876612	20071022
US 20080161349	A1	20080703	US 2007-928991	20071030

PRIORITY APPLN. INFO.:	US 1998-101542P	P	19980923
	US 1999-404001	A2	19990923
	CN 1999-812829	A3	19990923
	US 2000-502592	A	20000211
	WO 2001-US4168	W	20010209
	US 2001-8066	A3	20011105
	US 2003-644418	A3	20030820
	US 2003-695275	A3	20031028

OTHER SOURCE(S): MARPAT 141:174332
GI



I

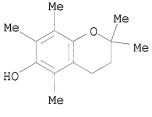
II

AB Chroman derivs., such as I [X = O, S, NR6; Y = O, NR6; R1 = carboxyalkyl, carboxyalkenyl, etc.; R2, R3, R4 = H, Me, alkyl, etc.; R5 = alkyl, alkenyl, etc.; R6 = H, alkyl], were prepared for use in antitumor pharmaceutical compns. for inducing apoptosis in a cell, particularly a cancer cell. Thus, α-tocopherol derivative II was prepared in 88% yield by a reaction of BrCH2CO2Me with (R,R,R)-α-tocopherol using NaOH in DMF. The prepared chromans were assayed for growth inhibitory and apoptotic activity against a variety of human cancer cell lines.

IT 950-99-2, 2,2,5,7,8-Pentamethyl-6-chromanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tocopherols, tocotrienols, other chroman and side chain derivs. for therapeutic use in prevention and treatment of cancer)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:665773 CAPLUS

DOCUMENT NUMBER: 140:52950

TITLE: Androgen Antagonist Activity by the Antioxidant Moiety of Vitamin E, 2,2,5,7,8-Pentamethyl-6-chromanol in Human Prostate Carcinoma Cells

AUTHOR(S): Thompson, Todd A.; Wilding, George

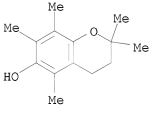
CORPORATE SOURCE: University of Wisconsin Comprehensive Cancer Center and University of Wisconsin Department of Medicine, University of Wisconsin-Madison, Madison, WI, 53792, USA

SOURCE: Molecular Cancer Therapeutics (2003), 2(8), 797-803
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Antioxidants, such as vitamin E, are being investigated for efficacy in prostate cancer prevention. In this study, we show that the antioxidant moiety of vitamin E, 2,2,5,7,8-pentamethyl-6-chromanol (PMCol), has antiandrogen activity in prostate carcinoma cells. In the presence of PMCol, the androgen-stimulated biphasic growth curve of LNCaP human prostate carcinoma cells was shifted to the right. The PMCol-induced growth shift was similar to that produced by treatment with the pure antiandrogen bicalutamide (i.e., Casodex), indicative of androgen receptor (AR) antagonist activity. The concentration of PMCol used was below the concentration required to affect cell growth or viability in the absence of androgen. Using an AR binding competition assay, PMCol was found to be a potent antiandrogen in both LNCaP and LAPC4 cells, with an IC50 of approx. 10 μM against 1 nM R1881 (methyltrienolone; a stable, synthetic androgen). Prostate-specific antigen release from LNCaP cells produced by androgen exposure with either 0.05 or 1.0 nM R1881 was inhibited 100% and 80%, resp., by 30 μM PMCol. Also, PMCol inhibited androgen-induced promoter activation in both LNCaP and LAPC4 cells. However, PMCol did not affect AR protein levels, suggesting that the inhibitory effects of PMCol on androgenic pathways were not due to decreased expression of the AR. Therefore, growth modulation by the antioxidant moiety of vitamin E in androgen-sensitive prostate carcinoma cells is due, at least in part, to its potent antiandrogenic activity.

IT 950-99-2, 2,2,5,7,8-Pentamethyl-6-chromanol
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(androgen antagonist activity by the antioxidant moiety of vitamin E, 2,2,5,7,8-pentamethyl-6-chromanol in human prostate carcinoma cells)

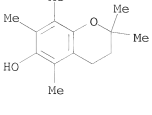
RN 950-99-2 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:126604 CAPLUS
DOCUMENT NUMBER: 139:63273
TITLE: Direct evidence for recycling of myeloperoxidase-catalyzed phenoxyl radicals of a vitamin E homologue, 2,2,5,7,8-pentamethyl-6-hydroxy chromane, by ascorbate/dihydrolipoate in living HL-60 cells
AUTHOR(S): Kagan, V. E.; Kuzmenko, A. I.; Shvedova, A. A.; Kisin, E. R.; Li, R.; Martin, I.; Quinn, P. J.; Tyurin, V.

A.; Tyurina, Y. Y.; Yalowich, J. C.
CORPORATE SOURCE: Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA, 15260, USA
SOURCE: Biochimica et Biophysica Acta, General Subjects (2003), 1620(1-3), 72-84
CODEN: BBGSB3; ISSN: 0304-4165
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Myeloperoxidase (MPO)-catalyzed one-electron oxidation of endogenous phenolic constituents (e.g., antioxidants, hydroxylated metabolites) and exogenous compds. (e.g., drugs, environmental chems.) generates free radical intermediates: phenoxyl radicals. Reduction of these intermediates by endogenous reductants, i.e. recycling, may enhance their antioxidant potential and/or prevent their potential cytotoxic and genotoxic effects. The goal of this work was to determine whether generation and recycling of MPO-catalyzed phenoxyl radicals of a vitamin E homolog, 2,2,5,7,8-pentamethyl-6-hydroxychromane (PMC), by physiol. relevant intracellular reductants such as ascorbate/lipoate could be demonstrated in intact MPO-rich human leukemia HL-60 cells. A model system was developed to show that MPO/H2O2-catalyzed PMC phenoxyl radicals (PMC$\sqrt{}$) could be recycled by ascorbate or ascorbate/dihydrolipoic acid (DHLA) to regenerate the parent compound Absorbance measurements demonstrated that ascorbate prevents net oxidation of PMC by recycling the phenoxyl radical back to the parent compound The presence of DHLA in the reaction mixture containing ascorbate extended the recycling reaction through regeneration of ascorbate. DHLA alone was unable to prevent PMC oxidation These conclusions were confirmed by direct detection of PMC$\sqrt{}$ and ascorbate radicals formed during the time course of the reactions by EPR spectroscopy. Based on results in the model system, PMC$\sqrt{}$ and ascorbate radicals were identified by EPR spectroscopy in ascorbate-loaded HL-60 cells after addition of H2O2 and the inhibitor of catalase, 3-aminotriazole (3-AT). The time course of PMC$\sqrt{}$ and ascorbate radicals was found to follow the same reaction sequence as during their recycling in the model system. Recycling of PMC by ascorbate was also confirmed by HPLC assays in HL-60 cells. Pre-loading of HL-60 cells with lipoic acid regenerated ascorbate and thus increased the efficiency of ascorbate in recycling PMC$\sqrt{}$. Lipoic acid had no effect on PMC oxidation in the absence of ascorbate. Thus PMC phenoxyl radical does not directly oxidize thiols but can be recycled by dihydrolipoate in the presence of ascorbate. The role of phenoxyl radical recycling in maintaining antioxidant defense and protecting against cytotoxic and genotoxic phenolics is discussed.
IT 950-99-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(direct evidence for recycling of myeloperoxidase-catalyzed phenoxyl radicals of a vitamin E homolog, 2,2,5,7,8-pentamethyl-6-hydroxy chromane, by ascorbate/dihydrolipoate in living HL-60 cells)
RN 950-99-2 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

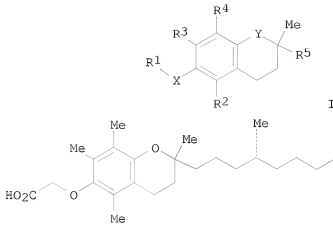
L8 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:595501 CAPLUS
DOCUMENT NUMBER: 137:140656
TITLE: Preparation of tocopherols, tocotrienols, other chromans and side chain derivs. as potential antiproliferative and proapoptotic agents
INVENTOR(S): Sanders, Bob G.; Kline, Kimberly; Yu, Weiping
PATENT ASSIGNEE(S): Research Development Foundation, USA
SOURCE: U.S. Pat. Appl. Publ., 44 pp., Cont.-in-part of U. S. Ser. No. 502,592.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20020107207	A1	20020808	US 2001-8066	20011105
US 6703384	B2	20040309		
US 6417223	B1	20020709	US 1999-404001	19990923
CN 1706838	A	20051214	CN 2005-10003855	19990923
CN 1318413	C	20070530		
US 6770672	B1	20040803	US 2000-502592	20000211
WO 2003039461	A2	20030515	WO 2002-US35147	20021101
WO 2003039461	A3	20031113		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002353971	A1	20030519	AU 2002-353971	20021101
US 20040097431	A1	20040520	US 2003-695275	20031028
US 7300954	B2	20071127		
US 20080161349	A1	20080703	US 2007-928991	20071030

PRIORITY APPLN. INFO.:

US 1998-101542P	P	19980923
US 1999-404001	A2	19990923
US 2000-502592	A2	20000211
CN 1999-812829	A3	19990923
US 2001-8066	A	20011105
WO 2002-US35147	W	20021101
US 2003-695275	A3	20031028

OTHER SOURCE(S): MARPAT 137:140656
GI

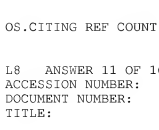


AB Derivs. of tocopherol, tocotrienol and other chromans of formula I (X and Y independently are oxygen, nitrogen or sulfur; when Y is nitrogen, nitrogen is substituted with R6 and R6 = H or Me; R1 = alkyl, alkenyl, alkynyl, aryl, heteroaryl, carboxylic acid, carboxylate, carboxamide, ester, thioamide, thiolacid, thiol ester, saccharide, alkoxy-linked saccharide, amine, sulfonate, sulfate, phosphate, alc., ethers or nitrites; R2, R3 = hydrogen or R4; R4 = Me, benzyl carboxylic acid, benzyl carboxylate, benzyl carboxamide, benzyl ester, saccharide or amine; and R5 = alkenyl) were prepared as antiproliferative and proapoptotic agents for the potential treatment of cell proliferative diseases. Thus, α-tocopherol was treated with Me bromoacetate and NaOH in N, N-dimethylformamide to give II. II showed effective growth inhibitory properties (apoptotic inducing) in a wide variety of human cancer cell lines, including breast, prostate, cervical, and ovarian cancers with EC50 values ranging from 1-20 μg/mL.

IT 950-99-2, 2,2,5,7,8-Pentamethyl-6-chromanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tocopherols, tocotrienols, other chromans and side chain derivs. as potential antiproliferative, proapoptotic agents for the treatment of cancer)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L8 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:597976 CAPLUS
DOCUMENT NUMBER: 135:166941
TITLE: Preparation of tocopherols, tocotrienols, other chroman and side chain derivatives that induce cell

apoptosis for therapeutic use as antiproliferative agents

INVENTOR(S): Sanders, Robert G.; Kline, Kimberly; Hurley, Laurence; Gardner, Robb; Menchaca, Marla; Yu, Weiping; Ramanan, Puthucode N.; Liu, Shenquan; Israel, Karen

PATENT ASSIGNEE(S): Research Development Foundation, USA

SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

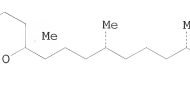
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001058889	A1	20010816	WO 2001-US4168	20010209
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6770672	B1	20040803	US 2000-502592	20000211
CA 2399802	A1	20010816	CA 2001-2399802	20010209
EP 1254130	A1	20021106	EP 2001-909008	20010209
EP 1254130	B1	20080102		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004504268	T	20040212	JP 2001-558439	20010209
NZ 520798	A	20040528	NZ 2001-520798	20010209
AU 2001236805	B2	20050714	AU 2001-236805	20010209
RU 2263672	C2	20051110	RU 2002-124135	20010209
IL 151108	A	20060801	IL 2001-151108	20010209
KR 847678	B1	20080723	KR 2002-710387	20020810

PRIORITY APPLN. INFO.:

US 2000-502592	A	20000211
US 1998-101542P	P	19980923
US 1999-404001	A2	19990923
WO 2001-US4168	W	20010209

OTHER SOURCE(S): MARPAT 135:166941

GI



I

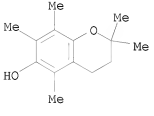
II

AB Tocopherol analogs, such as I [X = O, NH, S; Y = O, NH, S; R1 = alkyl, alkenyl, alkynyl, aryl, heteroaryl, carboxyl, carboxamide, thiocarboxyl, etc.; R2, R3, R4 = H, Me, benzyl, carboxyl, carboxamide, amine, saccharide; R5 = alkyl, alkenyl, alkynyl, aryl, heteroaryl, carboxyl, carboxamide], were prepared for pharmaceutical use as antiproliferative agents which induce cell apoptosis for treatment of cancers and diseases involving cell proliferation, such as autoimmune diseases, psoriasis, etc.. Thus, (R,R,R)-α-tocopherol derivative II was prepared in 88% yield by condensation of (R,R,R)-α-tocopherol and BrCH2CO2Me in DMF using NaOH followed by hydrolysis with 5 N HCl. The prepared tocopherol analogs were tested for their ability to induce apoptosis in a number of cancer cell lines, such as breast, cervical, colon, prostate, etc.

IT 950-99-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tocopherols, tocotrienols, other chromans that induce cell apoptosis for therapeutic use as antiproliferative agents)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2000:209907 CAPLUS

DOCUMENT NUMBER: 132:237223

TITLE: Preparation of tocopherols, tocotrienols, other chroman and side chain derivatives for use as antitumor agents and for inducing cell apoptosis

INVENTOR(S): Kline, Kimberly; Sanders, Bob G.; Hurley, Laurence; Gardner, Robb; Menchaca, Marla; Yu, Weiping; Ramanan, Puthucode N.; Liu, Shenquan; Israel, Karen

PATENT ASSIGNEE(S): Research Development Foundation, USA

SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000016772	A1	20000330	WO 1999-US21778	19990923
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2345079	A1	20000330	CA 1999-2345079		19990923
AU 9961553	A	20000410	AU 1999-61553		19990923
AU 757013	B2	20030130			
EP 1115398	A1	20010718	EP 1999-948352		19990923
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
CN 1325303	A	20011205	CN 1999-812829		19990923
CN 1195513	C	20050406			
JP 2002526446	T	20020820	JP 2000-573733		19990923
NZ 510732	A	20040130	NZ 1999-510732		19990923
RU 2232758	C2	20040720	RU 2001-111019		19990923
CN 1706838	A	20051214	CN 2005-10003855		19990923
CN 1318413	C	20070530			
IL 142082	A	20051218	IL 1999-142082		19990923
TW 592695	B	20040621	TW 1999-88120073		19991117
ZA 2001002057	A	20020319	ZA 2001-2057		20010313
PRIORITY APPLN. INFO.:			US 1998-101542P	P	19980923
			CN 1999-812829	A3	19990923
			WO 1999-US21778	W	19990923

OTHER SOURCE(S): MARPAT 132:237223

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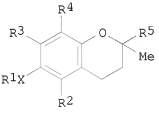
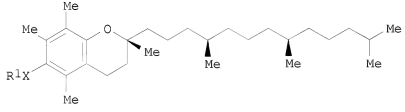


I



II

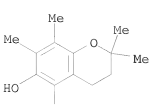
AB Chromans I [R1 = alkyl, alkenyl, alkynyl, aryl, herteroaryl, carboxyl, carboxamide, thioamide, saccharide, amine, sulfate, phosphate, etc.; R2, R3, R4 = H, Me, benzylcarboxylate, saccharide, amino, etc.; R5 = alkyl, alkenyl, alkynyl, aryl, herteroaryl, carboxyl, carboxamide; X = O, NH, S] were prepared for pharmaceutical use as antitumor agents and cell apoptosis inducing agents. Thus, tocopherol derivative II (R1 = CH2CO2H, X = O) was prepared in 88% yield via O-alkylation of (+)-α-tocopherol with Me bromoacetate. The prepared chromans were tested for cell apoptosis activity against a variety of cancer cell lines.

IT 950-99-2

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tocopherols, tocotrienols, other chroman and side chain derivs. for use as antitumor agents and for inducing cell apoptosis)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

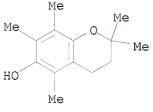
L8 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:602318 CAPLUS
DOCUMENT NUMBER: 131:295249
TITLE: Mechanism-based chemopreventive strategies against etoposide-induced acute myeloid leukemia: free radical/antioxidant approach
AUTHOR(S): Kagan, Valerian E.; Yalowich, Jack C.; Borisenko, Grigory G.; Tyurina, Yulia Y.; Tyurin, Vladimir A.; Thampatty, Padmakumari; Fabisiak, James P.
CORPORATE SOURCE: Departments of Environmental and Occupational Health and Pharmacology and University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA, USA
SOURCE: Molecular Pharmacology (1999), 56(3), 494-506
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Etoposide (VP-16) is extensively used to treat cancer, yet its efficacy is calamitously associated with an increased risk of secondary acute myelogenous leukemia. The mechanisms for the extremely high susceptibility of myeloid stem cells to the leukemogenic effects of etoposide have not been elucidated. We propose a mechanism to account for the etoposide-induced secondary acute myelogenous leukemia and nutritional strategies to prevent this complication of etoposide therapy. We hypothesize that etoposide phenoxyl radicals (etoposide-O) formed from etoposide by myeloperoxidase are responsible for its genotoxic effects in bone marrow progenitor cells, which contain constitutively high myeloperoxidase activity. Here, we used purified human myeloperoxidase, as well as human leukemia HL60 cells with high myeloperoxidase activity and provide evidence of the following. 1. Etoposide undergoes one-electron oxidation to etoposide-O· catalyzed by both purified myeloperoxidase and myeloperoxidase activity in HL60 cells; formation of etoposide-O·radicals is completely blocked by myeloperoxidase inhibitors, cyanide and azide. 2. Intracellular reductants, GSH and protein sulfhydryls (but not phospholipids), are involved in myeloperoxidase-catalyzed etoposide redox-cycling that oxidizes endogenous thiols; pretreatment of HL60 cells with a maleimide thiol reagent, ThioGlo1, prevents redox-cycling of etoposide-O· radicals and permits their direct ESR detection in cell homogenates. VP-16 redox-cycling by purified myeloperoxidase (in the presence of GSH) or by myeloperoxidase activity in HL60 cells is accompanied by generation of thiyl radicals, GS·, determined by HPLC assay of 5,5-dimethyl-1-pyrroline glytathionyl N-oxide glytathionyl nitrone adducts. 3. Ascorbate directly reduces etoposide-O·, thus competitively inhibiting etoposide-O·-induced thiol oxidation Ascorbate also diminishes etoposide-induced topo II-DNA complex formation

in myeloperoxidase-rich HL60 cells (but not in HL60 cells with myeloperoxidase activity depleted by pretreatment with succinyl acetone). 4. A vitamin E homolog, 2,2,5,7,8-pentamethyl-6-hydroxychromane, a hindered phenolic compound whose phenoxyl radicals do not oxidize endogenous thiols, effectively competes with etoposide as a substrate for myeloperoxidase, thus preventing etoposide-O·-induced redox-cycling. We conclude that nutritional antioxidant strategies can be targeted at minimizing etoposide conversion to etoposide-O·, thus minimizing the genotoxic effects of the radicals in bone marrow myelogenous progenitor cells, i.e., chemoprevention of etoposide-induced acute myelogenous leukemia.

IT 950-99-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism-based chemopreventive strategies against etoposide-induced acute myeloid leukemia: free radical/antioxidant approach)

RN 950-99-2 CAPLUS
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 43 THERE ARE 43 CAPLUS RECORDS THAT CITE THIS RECORD (43 CITINGS)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1995:497124 CAPLUS
DOCUMENT NUMBER: 122:255457
ORIGINAL REFERENCE NO.: 122:46305a,46308a
TITLE: Phenoxyl radicals of etoposide (VP-16) can directly oxidize intracellular thiols: protective versus damaging effects of phenolic antioxidants
AUTHOR(S): Tyurina, Yulla Y.; Tyurin, Vladimir; Yalowich, Jack C.; Quinn, Peter J.; Claycamp, H. Gregg; Schor, Nina F.; Pitt, Bruce R.; Kagan, Valerian E.
CORPORATE SOURCE: Departments Environmental Occupational Health, Univ. Pittsburgh, Pittsburgh, PA, 15238, USA
SOURCE: Toxicology and Applied Pharmacology (1995), 131(2), 277-88
CODEN: TXAPA9; ISSN: 0041-008X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

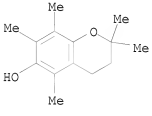
AB Phenolic compds. can act as radical scavengers due to their ability to donate a mobile hydrogen to peroxyl radicals producing a phenoxyl radical if the phenoxyl radical formed in the radical scavenging reaction efficiently interacts with vitally important biomols., then this interaction may result in cytotoxic effects rather than in antioxidant protection. In the present work we have chosen two model compds. a phenolic antitumor drug. VP-16, known to be highly cytotoxic, and a homolog of vitamin E, 2,2,5,7,8-pentamethyl-6-hydroxychromane (PMC)

as typical representatives of phenoxyl radicals to study interactions of their phenoxyl radicals with intracellular thiols. The results of this study suggest that the differential effects of PMC and VP-16 in intracellular environments, antioxidant protection or cytotoxicity, may be due, at least in part, to a striking difference in the reactivity of their resp. phenoxyl radicals toward endogenous thiols. In addition to their radical scavenging activity, the reactivity of phenoxyl radicals toward critical biomols. should be carefully considered in the design and development of biomedical antioxidants.

IT 950-99-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(phenoxyl radicals of etoposide (VP-16) can directly oxidize intracellular thiols: protective vs. damaging effects of phenolic antioxidants)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)

L8 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1993:440374 CAPLUS

DOCUMENT NUMBER: 119:40374

ORIGINAL REFERENCE NO.: 119:7147a,7150a

TITLE: Inhibition of NF-κB activation by vitamin E derivatives

AUTHOR(S): Suzuki, Yuichiro J.; Packer, Lester

CORPORATE SOURCE: Dep. Mol. Cell Biol., Univ. California, Berkeley, CA, 94720, USA

SOURCE: Biochemical and Biophysical Research Communications (1993), 193(1), 277-83
CODEN: BBRCA9; ISSN: 0006-291X

DOCUMENT TYPE: Journal

LANGUAGE: English

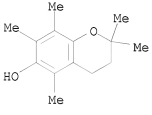
AB Nuclear factor κB (NF-κB) is believed to play an important role in the activation of a human immunodeficiency virus (HIV) which causes acquired immunodeficiency syndrome (AIDS). Recent findings suggesting an involvement of reactive oxygen species in signal transduction pathways leading to NF-κB activation have ensured the possible clin. use of antioxidants in blocking HIV activation. The present study examined the effects of vitamin E derivs. on the tumor necrosis factor-α (TNF-α)-induced NF-κB activation. Incubation of human Jurkat T cells with vitamin E acetate or α-tocopheryl succinate (10 μM to 1 mM) exhibited a concentration-dependent inhibition of NK-κB activation. α-Tocopherol or succinate at these concns. had no apparent effects. 2,2,5,7,8-Pentamethyl-6-hydroxychromane (PMC) was extremely effective, causing complete inhibition of NK-κB activation at 10 μM. Oct-1 binding activity was inactivated by α-tocopheryl succinate whereas other derivs. had no effects, suggesting that the effects of

α-tocopheryl succinate are not specific to NF-κB. HPLC measurements demonstrated that treatment of cells with TNF-α had no effects on cellular α-tocopherol, but vitamin E acetate treatment increased the α-tocopherol content. Cell viability was not affected by any of the vitamin E derivs. These results indicate a possible use of vitamin E derivs. in AIDS therapeutics.

IT 950-99-2
RL: BIOL (Biological study)
(TNF-α-induced nuclear factor κB activation inhibition by, AIDS therapy in relation to)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 142 THERE ARE 142 CAPLUS RECORDS THAT CITE THIS RECORD (142 CITINGS)

L8 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1991:101370 CAPLUS

DOCUMENT NUMBER: 114:101370

ORIGINAL REFERENCE NO.: 114:17269a,17272a

TITLE: Preparation of oxidized diphenylheteroalkanes as drugs and cosmetics

INVENTOR(S): Janssen, Bernd; Wuest, Hans Heiner

PATENT ASSIGNEE(S): BASF A.-G., Germany

SOURCE: Ger. Offen., 20 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3903988	A1	19900830	DE 1989-3903988	19890210
CA 2008401	A1	19900810	CA 1990-2008401	19900123
US 5128479	A	19920707	US 1990-471886	19900129
EP 386451	A1	19900912	EP 1990-101943	19900201
EP 386451	B1	19930428		
R: AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE				
AT 88699	T	19930515	AT 1990-101943	19900201
AU 9049266	A	19900816	AU 1990-49266	19900209
AU 621453	B2	19920312		
JP 03197446	A	19910828	JP 1990-28615	19900209
ZA 9000966	A	19911030	ZA 1990-966	19900209
KR 130059	B1	19980409	KR 1990-1624	19900210

PRIORITY APPLN. INFO.: DE 1989-3903988 A 19890210
EP 1990-101943 A 19900201

OTHER SOURCE(S): CASREACT 114:101370; MARPAT 114:101370

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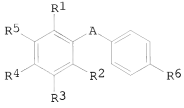

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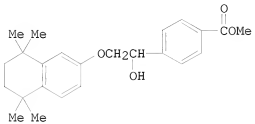


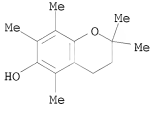
III

AB Title compds. I [A = CH(OH)CH2X or COCH2X (X = O, SO, SO2 or NH, and X is bound to either Ph ring); R1, R2, R3 = H, C1-4 alkyl; R4, R5 = H, C1-5 alkyl, or R4R5 = CMe2BCMe2 [B = (CH2)2 or CHMe], OCMeZCH2 [Z = (substituted) alkyl], or R4 = OR7 [R7 = H, (substituted) alkyl]; R6 = H, Me, cyano, tetrazolyl, SO3H, OH, substituted hydroxymethyl, amino, or aminomethyl, etc.], useful as drugs and cosmetics (no data), were prepared For example, epoxidn. of 4-formylbenzoic acid Me ester by trimethylsulfoxonium iodide gave phenyloxirane-4-carboxylic acid Me ester (II). Subsequent reaction of II with 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthol, obtained by Friedel-Crafts alkylation of PhOH, gave title compound III. The pharmaceutical formulation of III was described.

IT 950-99-2P, 2,2,5,7,8-Pentamethylchroman-6-ol
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of drugs)

RN 950-99-2 CAPLUS

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,2,5,7,8-pentamethyl- (CA INDEX NAME)



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

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L4            0 S L2 SSS
L5           12 S L2 FULL

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FULL ESTIMATED COST                                   103.20     320.21

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                    -13.12     -13.12

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=> s 15
L9          299 L5

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L10          10 L9 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)

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PROCESSING COMPLETED FOR L10
L11           8 DUP REM L10 (2 DUPLICATES REMOVED)

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In a multifile environment, a format can only be used if it is valid
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individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):ibib abs

L11  ANSWER 1 OF 8  EMBASE  COPYRIGHT (c) 2009 Elsevier B.V. All rights
     reserved on STN
ACCESSION NUMBER:   2009134386  EMBASE
TITLE:              In vitro assessment of P450 induction potential of novel
                    chemopreventive agents SR13668, 9-cis-UAB30, and
                    pentamethychromanol in primary cultures of human
                    hepatocytes.
AUTHOR:             Jackson, Jonathan P.
CORPORATE SOURCE:   CellzDirect/Invitrogen Corporation, Austin, TX 78754,
                    United States.
AUTHOR:             Kabirov, Kasim K.; Lyubimov, Alexander (correspondence)
CORPORATE SOURCE:   Toxicology Research Laboratory, College of Medicine,
                    University at Illinois at Chicago, Chicago, IL 60612,
                    United States. lyubimov@uic.edu
AUTHOR:             Kapetanovic, Izet M.
CORPORATE SOURCE:   Chemopreventive Agent Development Research Group, Division
                    of Cancer Prevention, National Cancer Institute, Bethesda,
```

MD 20892, United States.
SOURCE: Chemico-Biological Interactions, (15 May 2009) Vol. 179, No. 2-3, pp. 263-272.
Refs: 29
ISSN: 0009-2797 CODEN: CBINA8
PUBLISHER: Elsevier Ireland Ltd, P.O. Box 85, Limerick, Ireland.
PUBLISHER IDENT.: S 0009-2797(08)00667-4
COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Apr 2009
Last Updated on STN: 2 Apr 2009

AB Several compounds, including 2,10-dicarbethoxy-6-methoxy-5,7-dihydroindolo[2,3-b]carbazole (SR13668), (2E,4E,6Z,8E)-8-(3',4'-dihydro-1'(2'H)-napthalen-1'-ylidene)-3,7-dimethyl-2,4,6-octatrienoic acid (9-cis-UAB30), and 2,2,5,7,8-pentamethyl-6-chromanol (PMCol), were selected as promising chemopreventive agents and have entered preclinical trials for cancer prevention. The potential for adverse drug events resulting from interactions with other administered drugs, food components, or food additives presents an important question. Among the most important drug-drug interactions (DDI) is the potential of a new chemical entity (NCE) to induce cytochrome P450 enzymes (P450). Drug induction of P450 enzymes can lead to adverse drug interactions by increasing the metabolism of other drugs that are substrates for the induced isoform. Currently, sandwich cultured primary human hepatocytes are the standard for predicting human P450 enzyme induction in vitro as these cells retain the ability to respond to prototypical P450 inducers with the same specificity and potency exhibited in vivo. Therefore, a select panel of inducible P450 target genes (CYP1A2, CYP2B6, and CYP3A4) and their induction activity (measured by LC-MS/MS of respective marker substrate metabolites) were monitored in cultured hepatocytes following treatment with SR13668, 9-cis-UAB30, or PMCol to predict clinically significant drug-induced expression. The concentration ranges of the NCE used were selected to maximize the clinical relevance of these results. All responses were evaluated according to major prototypical P450 inducers (i.e., 3-methylcholanthrene, 3-MC; phenobarbital, PB; rifampicin, RIF) and increases ≥40% of the respective positive control(s) were considered an indication of demonstrable induction. Herein, we report that there is low potential for DDI with SR13668 and PMCol due to enzyme induction of CYP1A2, CYP2B6, and CYP3A4 expression at the concentrations examined. Similarly, the study results suggested that 9-cis-UAB30 has low potential to induce CYP1A2 and CYP3A4 expression at the concentrations examined. However, 9-cis-UAB30 was shown to significantly induce CYP2B6 enzyme activity at 10 μM suggesting the potential for DDI as a result.

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In a multifile environment, a format can only be used if it is valid
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individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):ibib abs

L11 ANSWER 1 OF 8 EMBASE

ACCESSION NUMBER: 2009134386 EMBASE
TITLE: In vitro assessment of P450 induction potential of novel chemopreventive agents SR13668, 9-cis-UAB30, and pentamethychromanol in primary cultures of human hepatocytes.
AUTHOR: Jackson, Jonathan P.
CORPORATE SOURCE: CellzDirect/Invitrogen Corporation, Austin, TX 78754, United States.
AUTHOR: Kabirov, Kasim K.; Lyubimov, Alexander (correspondence)
CORPORATE SOURCE: Toxicology Research Laboratory, College of Medicine, University at Illinois at Chicago, Chicago, IL 60612, United States. lyubimov@uic.edu
AUTHOR: Kapetanovic, Izet M.
CORPORATE SOURCE: Chemopreventive Agent Development Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD 20892, United States.
SOURCE: Chemico-Biological Interactions, (15 May 2009) Vol. 179, No. 2-3, pp. 263-272.
Refs: 29
ISSN: 0009-2797 CODEN: CBINA8
PUBLISHER: Elsevier Ireland Ltd, P.O. Box 85, Limerick, Ireland.
PUBLISHER IDENT.: S 0009-2797(08)00667-4
COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Apr 2009
Last Updated on STN: 2 Apr 2009
AB Several compounds, including 2,10-dicarbethoxy-6-methoxy-5,7-dihydroindolo[2,3-b]carbazole (SR13668), (2E,4E,6Z,8E)-8-(3',4'-dihydro-1'(2'H)-napthalen-1'-ylidene)-3,7-dimethyl-2,4,6-octatrienoic acid (9-cis-UAB30), and 2,2,5,7,8-pentamethyl-6-chromanol (PMCol), were selected as promising chemopreventive agents and have entered preclinical trials for cancer prevention. The potential for adverse drug events resulting from interactions with other administered drugs, food components, or food additives presents an important question. Among the most important drug-drug interactions (DDI) is the potential of a new chemical entity (NCE) to induce cytochrome P450 enzymes (P450). Drug induction of P450 enzymes can lead to adverse drug interactions by increasing the metabolism of other drugs that are substrates for the induced isoform. Currently, sandwich cultured primary human hepatocytes are the standard for predicting human P450 enzyme induction in vitro as these cells retain the ability to respond to prototypical P450 inducers with the same specificity and potency exhibited in vivo. Therefore, a select panel of inducible P450 target genes (CYP1A2, CYP2B6, and CYP3A4) and their induction activity (measured by LC-MS/MS of respective marker substrate metabolites) were monitored in cultured hepatocytes following treatment with SR13668, 9-cis-UAB30, or PMCol to predict clinically significant drug-induced expression. The concentration ranges of the NCE used were selected to maximize the clinical relevance of these results. All responses were evaluated according to major prototypical P450 inducers (i.e., 3-methylcholanthrene, 3-MC; phenobarbital, PB; rifampicin, RIF) and increases ≥40% of the respective positive control(s) were considered an indication of demonstrable induction. Herein, we report that there is low potential for DDI with SR13668 and PMCol due to enzyme induction of CYP1A2, CYP2B6, and CYP3A4 expression at the concentrations examined. Similarly, the study results suggested that 9-cis-UAB30 has low potential to induce CYP1A2 and CYP3A4 expression at the concentrations

examined. However, 9-cis-UAB30 was shown to significantly induce CYP2B6 enzyme activity at 10 μM suggesting the potential for DDI as a result. .COPYRGT. 2008 Elsevier Ireland Ltd.

L11 ANSWER 2 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2009006301 MEDLINE
DOCUMENT NUMBER: PubMed ID: 19074288
TITLE: Long-chain carboxychromanols, metabolites of vitamin E, are potent inhibitors of cyclooxygenases.
AUTHOR: Jiang Qing; Yin Xinmin; Lill Markus A; Danielson Matthew L; Freiser Helene; Huang Jianjie
CORPORATE SOURCE: Department of Foods and Nutrition, Interdepartmental Nutrition Program, Purdue University, West Lafayette, IN 47907, USA.. qjiang@purdue.edu
CONTRACT NUMBER: P01AT002620 (United States NCCAM NIH HHS)
R01AT001821 (United States NCCAM NIH HHS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2008 Dec 23) Vol. 105, No. 51, pp. 20464-9. Electronic Publication: 2008-12-11.
Journal code: 7505876. E-ISSN: 1091-6490.
Report No.: NLM-PMC2629323.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200901
ENTRY DATE: Entered STN: 2 Jan 2009
Last Updated on STN: 28 Jan 2009
Entered Medline: 27 Jan 2009

AB Cyclooxygenase (COX-1/COX-2)-catalyzed eicosanoid formation plays a key role in inflammation-associated diseases. Natural forms of vitamin E are recently shown to be metabolized to long-chain carboxychromanols and their sulfated counterparts. Here we find that vitamin E forms differentially inhibit COX-2-catalyzed prostaglandin E(2) in IL-1beta-stimulated A549 cells without affecting COX-2 expression, showing the relative potency of gamma-tocotrienol approximately delta-tocopherol > gamma-tocopherol >> alpha- or beta-tocopherol. The cellular inhibition is partially diminished by sesamin, which blocks the metabolism of vitamin E, suggesting that their metabolites may be inhibitory. Consistently, conditioned media enriched with long-chain carboxychromanols, but not their sulfated counterparts or vitamin E, reduce COX-2 activity in COX-preinduced cells with 5 microM arachidonic acid as substrate. Under this condition, 9'- or 13'-carboxychromanol, the vitamin E metabolites that contain a chromanol linked with a 9- or 13-carbon-length carboxylated side chain, inhibits COX-2 with an IC(50) of 6 or 4 microM, respectively. But 13'-carboxychromanol inhibits purified COX-1 and COX-2 much more potently than shorter side-chain analogs or vitamin E forms by competitively inhibiting their cyclooxygenase activity with K(i) of 3.9 and 10.7 microM, respectively, without affecting the peroxidase activity. Computer simulation consistently indicates that 13'-carboxychromanol binds more strongly than 9'-carboxychromanol to the substrate-binding site of COX-1. Therefore, long-chain carboxychromanols, including 13'-carboxychromanol, are novel cyclooxygenase inhibitors, may serve as anti-inflammation and anticancer agents, and may contribute to the beneficial effects of certain forms of vitamin E.

L11 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003400986 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12939470
TITLE: Androgen antagonist activity by the antioxidant moiety of vitamin E, 2,2,5,7,8-pentamethyl-6-chromanol in human

prostate carcinoma cells.

AUTHOR: Thompson Todd A; Wilding George

CORPORATE SOURCE: University of Wisconsin Comprehensive Cancer Center, University of Wisconsin-Madison, Madison, Wisconsin 53792, USA.

SOURCE: Molecular cancer therapeutics, (2003 Aug) Vol. 2, No. 8, pp. 797-803.
Journal code: 101132535. ISSN: 1535-7163.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200406

ENTRY DATE: Entered STN: 27 Aug 2003
Last Updated on STN: 24 Jun 2004
Entered Medline: 21 Jun 2004

AB Antioxidants, such as vitamin E, are being investigated for efficacy in prostate cancer prevention. In this study, we show that the antioxidant moiety of vitamin E, 2,2,5,7,8-pentamethyl-6-chromanol (PMCol), has antiandrogen activity in prostate carcinoma cells. In the presence of PMCol, the androgen-stimulated biphasic growth curve of LNCaP human prostate carcinoma cells was shifted to the right. The PMCol-induced growth shift was similar to that produced by treatment with the pure antiandrogen bicalutamide (i.e., Casodex), indicative of androgen receptor (AR) antagonist activity. The concentration of PMCol used was below the concentration required to affect cell growth or viability in the absence of androgen. Using an AR binding competition assay, PMCol was found to be a potent antiandrogen in both LNCaP and LAPC4 cells, with an IC(50) of approximately 10 micro M against 1 nM R1881 (methyltrienolone; a stable, synthetic androgen). Prostate-specific antigen release from LNCaP cells produced by androgen exposure with either 0.05 or 1.0 nM R1881 was inhibited 100% and 80%, respectively, by 30 micro M PMCol. Also, PMCol inhibited androgen-induced promoter activation in both LNCaP and LAPC4 cells. However, PMCol did not affect AR protein levels, suggesting that the inhibitory effects of PMCol on androgenic pathways were not due to decreased expression of the AR. Therefore, growth modulation by the antioxidant moiety of vitamin E in androgen-sensitive prostate carcinoma cells is due, at least in part, to its potent antiandrogenic activity.

L11 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:544811 BIOSIS

DOCUMENT NUMBER: PREV200300546374

TITLE: Industrial applications of Aspergillus carneus.

AUTHOR(S): Saxena, R. K. [Reprint Author]; Davidson, W. S. [Reprint Author]; Batra, A. [Reprint Author]; Malhotra, B. [Reprint Author]; Sheoran, A. [Reprint Author]

CORPORATE SOURCE: University of Delhi, South Campus, New Delhi, India

SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2003) Vol. 103, pp. O-125.
http://www.asmusa.org/mtgsrc/generalmeeting.htm. cd-rom.
Meeting Info.: 103rd American Society for Microbiology General Meeting. Washington, DC, USA. May 18-22, 2003.
American Society for Microbiology.
ISSN: 1060-2011 (ISSN print).

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 19 Nov 2003
Last Updated on STN: 19 Nov 2003

AB Lipases have proved versatile, efficient biocatalysts for wide ranges of

esterification, transesterification and ester hydrolysis reactions. The high chemo-, regio-, and stereo-selectivity and mild conditions of lipases- catalyzed reactions have led to the recognition of the vast potential of these biocatalysts for industrial applications. Our researches using Aspergillus carneus on lipase production have shown that it has great potential to produce an alkaline, thermostable lipase optimally active at pH 9.0 The lipase active over a wide temperature range of 20-70degreeC and has excellent pH tolerance and stability (6.0-12.0). The enzyme shows regioselective hydrolysis of peracetylated polyphenolic compounds. Two new compounds with potential as antitumour, antibiotic and anti oxidant drugs were synthesized using the chemo and regiospecific behaviour of this lipase. The lipase shows enatioselective synthesis of chromanols, pharmaceutically important compounds, diethyl acetamidomalonate, a precursor for synthesis of glutamic and aspartic acids and cyanohydrin of meta-phenoxybenzaldehyde, intermediate for several pyrethriod insecticides. Present lipase has a unique property of chemo- & regiospecific hydrolysis of acetophenones, benzophenones and amides and esters of polyacetoxy aromatic carboxylic acids, which can be exploited for the synthesis of pharmaceutically important drug intermediates. Aspergillus carneus lipase can mediate peptide synthesis between N - betaoc - methionine and different amino-acid methyl esters examined in both toluene and n-hexane. The enzyme also catalyzes enatioselective transesterification of the recemic esters of cyanohydrin and showed distinct preference for the S-enatiomer. Several industrially important flavor compounds, food-compatible emulsifiers, biosurfactant and anti-oxidants are produced by this lipase-mediated esterification. The lipase can be produced easily in protease free condition, which makes a very long shelf life of the enzyme at room temperature. The enzyme can be efficiently immobilized and reused.

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ACCESSION NUMBER: 1999303096 EMBASE

TITLE: Mechanism-based chemopreventive strategies against etoposide-induced acute myeloid leukemia: Free radical/antioxidant approach.

AUTHOR: Kagan, Valerian E., Dr. (correspondence); Borisenko, Grigory G.; Tyurina, Yulia Y.; Tyurin, Vladimir A.; Fabisiak, James P.

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SOURCE: Molecular Pharmacology, (1999) Vol. 56, No. 3, pp. 494-506. Refs: 42
ISSN: 0026-895X CODEN: MOPMA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article
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030 Clinical and Experimental Pharmacology
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005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Sep 1999
Last Updated on STN: 16 Sep 1999

AB Etoposide (VP-16) is extensively used to treat cancer, yet its efficacy is calamitously associated with an increased risk of secondary acute myelogenous leukemia. The mechanisms for the extremely high susceptibility of myeloid stem cells to the leukemogenic effects of etoposide have not been elucidated. We propose a mechanism to account for the etoposide-induced secondary acute myelogenous leukemia and nutritional strategies to prevent this complication of etoposide therapy. We hypothesize that etoposide phenoxyl radicals (etoposide-O.ovrhdot.) formed from etoposide by myeloperoxidase are responsible for its genotoxic effects in bone marrow progenitor cells, which contain constitutively high myeloperoxidase activity. Here, we used purified human myeloperoxidase, as well as human leukemia HL60 cells with high myeloperoxidase activity and provide evidence of the following. 1) Etoposide undergoes one-electron oxidation to etoposide-O.ovrhdot. catalyzed by both purified myeloperoxidase and myeloperoxidase activity in HL60 cells; formation of etoposide-O.ovrhdot. radicals is completely blocked by myeloperoxidase inhibitors, cyanide and azide. 2) Intracellular reductants, GSH and protein sulfhydryls (but not phospholipids), are involved in myeloperoxidase- catalyzed etoposide redox-cycling that oxidizes endogenous thiols; pretreatment of HL60 cells with a maleimide thiol reagent, ThioGlo1, prevents redox-cycling of etoposide-O.ovrhdot. radicals and permits their direct electron paramagnetic resonance detection in cell homogenates. VP-16 redox-cycling by purified myeloperoxidase (in the presence of GSH) or by myeloperoxidase activity in HL60 cells is accompanied by generation of thiyl radicals, GS.ovrhdot., determined by HPLC assay of 5,5-dimethyl-1-pyrroline glytathionyl N-oxide glytathionyl nitrone adducts. 3) Ascorbate directly reduces etoposide-O.ovrhdot., thus competitively inhibiting etoposide-O.ovrhdot.-induced thiol oxidation. Ascorbate also diminishes etoposide-induced topo II-DNA complex formation in myeloperoxidase-rich HL60 cells (but not in HL60 cells with myeloperoxidase activity depleted by pretreatment with succinyl acetone). 4) A vitamin E homolog, 2,2,5,7,8-pentamethyl-6-hydroxychromane, a hindered phenolic compound whose phenoxyl radicals do not oxidize endogenous thiols, effectively competes with etoposide as a substrate for myeloperoxidase, thus preventing etoposide-O.ovrhdot.-induced redox-cycling. We conclude that nutritional antioxidant strategies can be targeted at minimizing etoposide conversion to etoposide-O.ovrhdot., thus minimizing the genotoxic effects of the radicals in bone marrow myelogenous progenitor cells, i.e., chemoprevention of etoposide- induced acute myelogenous leukemia.

L11 ANSWER 6 OF 8 MEDLINE on STN
ACCESSION NUMBER: 1997228091 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9115995
TITLE: Reactions of phenoxyl radicals with NADPH-cytochrome P-450 oxidoreductase and NADPH: reduction of the radicals and inhibition of the enzyme.
AUTHOR: Goldman R; Tsyrlov I B; Grogan J; Kagan V E
CORPORATE SOURCE: Department of Environmental & Occupational Health, University of Pittsburgh, Pennsylvania 15238, USA.
SOURCE: Biochemistry, (1997 Mar 18) Vol. 36, No. 11, pp. 3186-92.

Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 6 May 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 21 Apr 1997

AB Phenoxyl radicals are intermediates of one-electron oxidation of phenolic compounds by various peroxidases. This report describes reactions of phenoxyl radicals with human NADPH-cytochrome P-450 oxidoreductase (OR) and NADPH. Purified truncated OR catalyzed quenching of EPR signal of the phenoxyl radical of a vitamin E homolog, 2,2,5,7,8-pentamethyl-6-hydroxychromane. The quenching required both reductase and NADPH and was not supported by NADH. NADPH quenched directly the EPR signal of phenoxyl radical of a phenolic antitumor drug, etoposide, in the absence of the OR. Quenching of the EPR signal was accompanied by increased rate of NADPH oxidation and decreased rate of etoposide oxidation. Phenoxyl radicals of etoposide did not inactivate the OR. In the absence of NADPH, OR was inhibited irreversibly when exposed to phenoxyl radicals of phenol. The activity of the flavoprotein could not be recovered by dithiothreitol (DTT) but the inhibition was prevented by saturation of OR with NADP+ prior to the exposure to phenoxyl radicals. The OR was also inhibited by 5,5'-dithionitrobenzoic acid (DTNB). The inhibition was reversible by subsequent addition of DTT. OR pretreated with DTNB was protected from inhibition by phenoxyl radicals of phenol. The results indicate that phenoxyl radical of 2,2,5,7,8-pentamethyl-6-hydroxychromane is likely reduced enzymatically by transfer of electrons from NADPH via the FAD/FMN of the OR. Phenoxyl radicals with higher redox potential, e.g., phenoxyl radicals of etoposide, oxidize NADPH directly. Phenoxyl radicals of phenol can also inactivate OR likely by oxidation of cysteine 565 in the NADPH binding region of the enzyme.

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ACCESSION NUMBER: 1996010794 EMBASE
TITLE: Oxidative stress mediates synthesis of cytosolic phospholipase A(2) after UVB injury.
AUTHOR: Chen, X.; Gresham, A.; Morrison, A.; Pentland, A.P. (correspondence)
CORPORATE SOURCE: Division of Dermatology, Department of Medicine, Washington Univ. School of Medicine, 660 South Euclid, Box 8123, St. Louis, MO 63110, United States.
SOURCE: Biochimica et Biophysica Acta - Lipids and Lipid Metabolism, (1996) Vol. 1299, No. 1, pp. 23-33. ISSN: 0005-2760 CODEN: BBLLA6
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jan 1996
Last Updated on STN: 27 Jan 1996

AB UVB irradiation has previously been shown to significantly increase phospholipase activity and prostaglandin synthesis. Because UVB irradiation is a potent oxidative stress, the role of active oxygen

species in regulating UV-induced cPLA(2) synthesis and phosphorylation was examined. In the present study, irradiation produced a 3-fold increase in synthesis within 6 h following irradiation. Phosphorylation of cPLA(2) was also increased to a similar extent. UVB-induced synthesis and phosphorylation of cPLA(2) could be inhibited by pretreatment with the antioxidants 2,2,5,7,8-pentamethyl-6-hydroxychromane (50 μM) or N-acetylcysteine (10 mM). Treatment of unirradiated cultures with the potent oxidant tert-butyl hydroperoxide (500 μM) also increased cPLA(2) synthesis and phosphorylation, suggesting that oxidative injury is an important regulator of cPLA(2) synthesis. Increased synthesis of cPLA(2) correlated well with increased [(3)H]arachidonic acid release, PGE(2) synthesis and lipid peroxidation in epidermis after oxidant or UVB treatment. The results indicate that UVB-induced upregulation of cPLA(2) synthesis is mediated by UVB-induced formation of free radicals.

L11 ANSWER 8 OF 8 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 1995232770 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7716769
TITLE: Phenoxyl radicals of etoposide (VP-16) can directly oxidize intracellular thiols: protective versus damaging effects of phenolic antioxidants.
AUTHOR: Tyurina Y Y; Tyurin V A; Yalowich J C; Quinn P J; Claycamp H G; Schor N F; Pitt B R; Kagan V E
CORPORATE SOURCE: Department of Environmental and Occupational Health, University of Pittsburgh, Pennsylvania 15238, USA.
SOURCE: Toxicology and applied pharmacology, (1995 Apr) Vol. 131, No. 2, pp. 277-88.
Journal code: 0416575. ISSN: 0041-008X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 24 May 1995
Last Updated on STN: 3 Feb 1997
Entered Medline: 18 May 1995

AB Phenolic compounds can act as radical scavengers due to their ability to donate a mobile hydrogen to peroxyl radicals producing a phenoxyl radical if the phenoxyl radical formed in the radical scavenging reaction efficiently interacts with vitally important biomolecules, then this interaction may result in cytotoxic effects rather than in antioxidant protection. In the present work we have chosen two model compounds--a phenolic antitumor drug, VP-16, known to be highly cytotoxic, and a homolog of vitamin E, 2,2,5,7,8-pentamethyl-6-hydroxychromane (PMC)--as typical representatives of phenoxyl radicals to study interactions of their phenoxyl radicals with intracellular thiols. Using a water-soluble source of peroxyl radicals, the azo-initiator 2,2'-azobis(2-aminodinopropane) (AAPH), we found that both PMC and VP-16 are very efficient scavengers of peroxyl radicals as evidenced by their ability to inhibit AAPH-induced chemiluminescence of luminol and oxidation of PnA incorporated into DOPC liposomes. Both PMC and VP-16 were also able to protect against AAPH-induced oxidative degradation of DNA in nuclei from human leukemic K562 cells. In contrast, there was a dramatic difference in the ability of VP-16 and PMC to protect GSH against AAPH-induced oxidation: while PMC inhibited AAPH-induced oxidation of GSH in a concentration-dependent manner, VP-16 did not protect GSH against oxidation. We hypothesized that this was due to different reactivities of the phenoxyl radicals formed by AAPH-derived peroxyl radicals from VP-16 and PMC toward GSH. To substantiate this hypothesis, we compared interactions of the phenoxyl radicals generated from VP-16 and PMC with

intracellular thiols in K562 cell homogenates. While the PMC phenoxyl radicals were only slightly affected by thiols, the VP-16 phenoxyl radicals were reduced by thiols. This is evidenced by (i) a significant inhibition of the tyrosinase-induced VP-16 consumption upon addition of K562 cell homogenates, (ii) a depletion of endogenous thiols in K562 cell homogenates induced by VP-16+tyrosinase, (iii) a transient disappearance of the VP-16 phenoxyl radical signal from the ESR spectra and its reappearance after depletion of endogenous thiols, and (iv) elimination of the lag period for the appearance of the VP-16 phenoxyl radical ESR signal subsequent to depletion of thiols by mersalyl acid. To evaluate the contribution of GSH and protein thiols to reduction of the VP-GSH-peroxidase + cumeme hydroperoxide to specifically deplete endogenous GSH.(ABSTRACT TRUNCATED AT 400 WORDS)

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=> d his

     (FILE 'HOME' ENTERED AT 17:01:14 ON 17 SEP 2009)

     FILE 'REGISTRY' ENTERED AT 17:01:24 ON 17 SEP 2009
L1             0 S PMCOL
L2               STRUCTURE UPLOADED
L3             0 S L2
L4             0 S L2 SSS
L5            12 S L2 FULL

     FILE 'CAPLUS' ENTERED AT 17:02:58 ON 17 SEP 2009
L6           442 S L5
L7            16 S L6 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)
L8            16 DUP REM L7 (0 DUPLICATES REMOVED)

     FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 17:07:46 ON 17 SEP 2009
L9           299 S L5
L10           10 S L9 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)
L11            8 DUP REM L10 (2 DUPLICATES REMOVED)

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